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Perspective

The neurobiology of long COVID

Michelle Monje[1,2,*] and Akiko Iwasaki[3,4,*]
[1]Department of Neurology, Stanford University, Stanford, CA 94305, USA
[2]Howard Hughes Medical Institute, Stanford University, USA
[3]Department of Immunobiology, Yale University, New Haven, CT 06520, USA
[4]Howard Hughes Medical Institute, Yale University, USA
*Correspondence: mmonje@stanford.edu (M.M.), akiko.iwasaki@yale.edu (A.I.)
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SUMMARY

Persistent neurological and neuropsychiatric symptoms affect a substantial fraction of people after COVID-19 and represent a major component of the post-acute COVID-19 syndrome, also known as long COVID. Here, we review what is understood about the pathobiology of post-acute COVID-19 impact on the CNS and discuss possible neurobiological underpinnings of the cognitive symptoms affecting COVID-19 survivors. We propose the chief mechanisms that may contribute to this emerging neurological health crisis.

INTRODUCTION

A wide range of neurological and neuropsychiatric symptoms are common features of acute COVID-19 (Helms et al., 2020; Mao et al., 2020; Varatharaj et al., 2020; Chou et al., 2021) and post-acute COVID-19 syndrome (PACS) (Nasserie et al., 2021), or long COVID. Long COVID describes a collection of prolonged symptoms that develop during or following a confirmed or suspected case of COVID-19, often following a mild infection (Davis et al., 2021). These acute and chronic neurological and neuropsychiatric symptoms include anosmia, ageusia, cognitive impairments, depression, and anxiety (Nasserie et al., 2021). Prominent among these lasting neurological sequelae is a syndrome of persistent cognitive impairment known as COVID-19 "brain fog," characterized by impaired attention, concentration, memory, speed of information processing, and executive function. Neuroinflammation alone can cause dysregulation of glial and neuronal cells and, ultimately, neural circuit dysfunction that negatively impacts cognitive and neuropsychiatric functions (for reviews, please see Wright-Jin and Gutmann, 2019; Gibson and Monje, 2021; Henn et al., 2022). Layered on top of the effects of immune-mediated neural cellular dysregulation are possible additional mechanisms of neural injury such as ischemia, nervous system infection, or cytotoxic immune reactions. In fact, many other viral, bacterial, and parasitic infections can lead to neurocognitive impairment in post-acute infection syndromes (PAISs) (Choutka et al., 2022). A subset of PAIS patients develops myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), a chronic and debilitating condition with neurological and immunological symptoms accompanied by chronic fatigue that is not relieved by sleep or rest. Similar to PAISs, neuroinflammatory mechanisms are central to a syndrome of cognitive impairment that frequently occurs after cancer therapy (Gibson and Monje, 2021). Understanding the mechanistic underpinnings of long COVID may help to elucidate unifying principles of nervous system pathobiology shared with other syndromes of neurological and neuropsychiatric dysfunction that can occur after infections and other immune challenges.

COVID-19 may affect the central nervous system in (at least) six main ways (Figure 1). First, the immune response to SARS-CoV-2 in the respiratory system may cause neuroinflammation—increasing cytokines, chemokines, and immune cell trafficking in the brain and inducing reactive states of resident microglia and other immune cells in the brain and brain borders. Second, SARS-CoV-2 rarely may directly infect the nervous system. Third, SARS-CoV-2 may evoke an autoimmune response against the nervous system. Fourth, reactivation of latent herpesviruses, like the Epstein-Barr virus, may trigger neuropathology. Fifth, cerebrovascular and thrombotic disease may disrupt blood flow, disrupt blood-brain-barrier function, and contribute to further neuroinflammation and/or ischemia of neural cells. Lastly, pulmonary and multi-organ dysfunction occurring in severe COVID-19 can cause hypoxemia, hypotension, and metabolic disturbances that can negatively affect neural cells. It is important to recognize that these mechanisms of nervous system injury are not mutually exclusive, and a combination of mechanisms may occur in some individuals, with varying frequency and timing. For example, neuroinflammation triggered by the immune response to the respiratory system infection and consequent dysregulation of neural homeostasis and plasticity is likely a more common mechanistic principle that occurs even after mild disease in the acute phase, while direct brain infection is likely an uncommon mechanism associated with severe COVID-19. Here, we will review what is known about the effects of COVID-19 on the brain after the acute phase of infection, each of these six mechanisms of COVID-19-induced neural injury, and open questions that remain to be addressed in the urgent efforts to elucidate the neurobiological underpinnings of long-COVID-associated cognitive impairment.

Neural-immune interactions and cognitive function

Cognitive function relies on the precise activity of neural circuits, which in turn depends upon finely regulated interactions of

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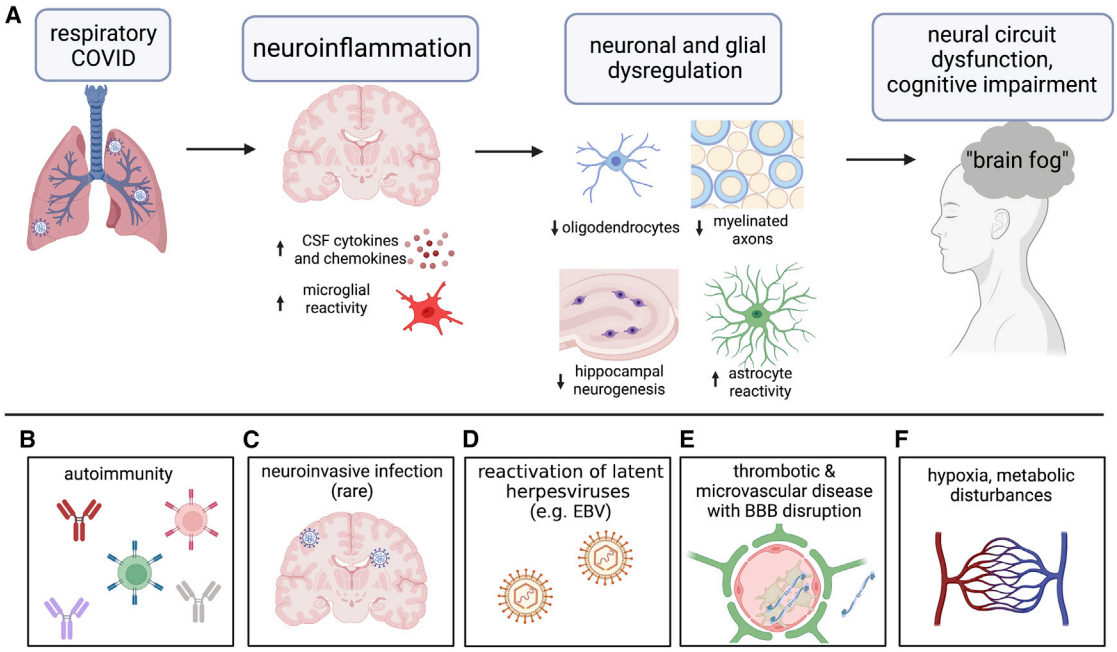

Figure 1. Possible mechanisms contributing to COVID-19-related cognitive impairment

(A) Respiratory system inflammation causes inflammation of the nervous system through systemic chemokines and other possible mechanisms. CNS cytokines, chemokines, and reactive microglia dysregulate multiple neural cell types, disrupt myelin homeostasis and plasticity, impair hippocampal neurogenesis, and induce neurotoxic astrocyte reactivity, each of which can impair neural circuit function and thus cognition.

(B) Anti-neural autoantibodies and T cells can cause autoimmune encephalitis in patients with COVID-19 and could contribute to ongoing immune-mediated injury.

(C) Neuroinvasive infection is rarely detected but can occur.

(D) COVID-19 can trigger reactivation of latent herpesvirus infections, most prominently EBV, which can in turn incite further inflammation.

(E) Neurovascular dysfunction, including blood-brain-barrier disruption (astrocyte endfeet, green) with consequent leakage of fibrinogen (blue linear molecule represented both intravascularly and in the extravascular space) and other pro-inflammatory molecules, and thrombosis (platelets, tan) can contribute to neural inflammation and injury.

(F) In severe COVID-19, hypoxia and other metabolic disturbances from pulmonary and multi-organ dysfunction can cause nervous system injury. Figure created with BioRender.

neurons with glial cells. In healthy, homeostatic states, astrocytes control the formation and function of synapses (Allen et al., 2012; Christopherson et al., 2005; Ullian et al., 2001) and promote hippocampal neurogenesis (Song et al., 2002), microglia regulate neuronal excitability (Badimon et al., 2020) and sculpt circuit connectivity (Schafer et al., 2012; Stevens et al., 2007), and myelinating oligodendrocytes tune circuit dynamics by modulating the speed of action potential conduction (Huxley and Stämpeli, 1949; Smith and Koles, 1970) and provide metabolic support to axons (Funfschilling et al., 2012). Neuron-glial interactions are dynamic and enable adaptive plasticity of synaptic strength (Stellwagen and Malenka, 2006), synaptic connectivity (Schafer et al., 2012), and myelination (Gibson et al., 2014) in many instances through mechanisms that are immunological in nature, such as complement-mediated engulfment of synapses by microglia (Stevens et al., 2007) and cytokine-mediated changes in synaptic strength (Stellwagen and Malenka, 2006). Such neural plasticity is thought to be central to cognitive functions, such as learning and memory.

Neural-circuit plasticity depends upon maintenance of healthy glial cells, which are profoundly influenced by interactions with each other (reviewed in Pan and Monje, 2020) and with the immune system (reviewed in Salvador et al., 2021). Microglia are resident myeloid-lineage immune cells that colonize the brain during early embryonic development (Ginhoux et al., 2010) and exhibit numerous distinct transcriptional and functional states throughout life (Hammond et al., 2019; Wright-Jin and Gutmann, 2019), some which promote cellular mechanisms of plasticity, including hippocampal neurogenesis (Butovsky et al., 2006) and myelin regeneration (Miron et al., 2013). Microglia are exquisitely responsive to immunological signals and rapidly assume reactive phenotypes in which these homeostatic and plasticity-promoting functions are lost. Microglial reactivity leads to secretion of cytokines and enhanced phagocytosis that is intended to limit the spread of pathogens, but when not properly regulated, can profoundly disrupt neural circuit regulation, function, and plasticity in ways that can contribute to cognitive impairment and neuropsychiatric diseases (Hong et al., 2016; Sekar et al., 2016). Reactive microglia and brain-infiltrating macrophages impair mechanisms of cellular homeostasis and plasticity such as maintenance and ongoing generation of myelin-forming oligodendrocytes (Gibson et al., 2019), myelin plasticity (Geraghty et al., 2019), and new neuron generation in the hippocampus in rodents (Monje et al., 2002, 2003; Ekdahl et al., 2003) and in humans (Monje et al., 2007) (Figure 2).

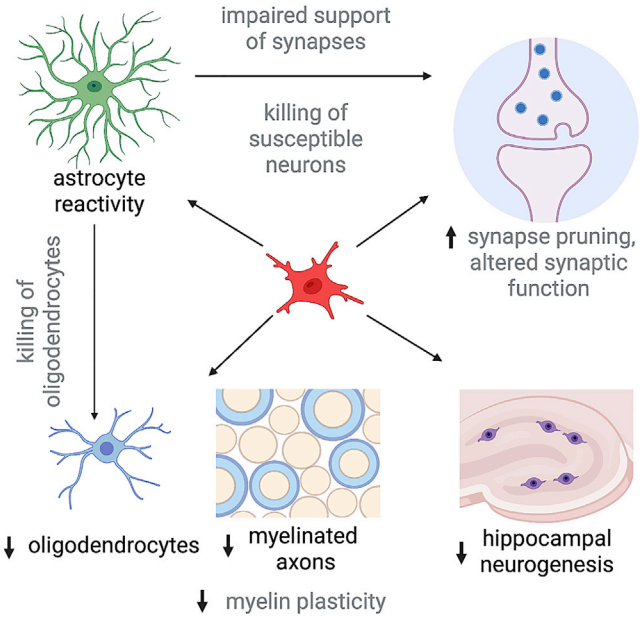

Figure 2. Demonstrated (black text) and hypothesized (gray text) downstream consequences of reactive microglia in neuro-COVID

Reactive microglia (red) can induce complex cellular dysregulation affecting neurons and oligodendrocytes. Demonstrated effects of reactive microglia after COVID-19 include a reduction in oligodendrocytes (blue) and myelinated axons, highlighting disrupted myelin (blue) homeostasis. Myelin plasticity—the capacity of oligodendroglial lineage cells to respond to neuronal activity with adaptive changes in myelin that tune circuit function— may also be impaired as occurs in other disease settings, but this remains to be demonstrated in the context of the post-COVID-19 brain. Reactive microglia may induce neurotoxic astrocyte reactivity —demonstrated in cases of severe COVID-19 and yet to be evaluated after mild COVID-19. Reactive astrocytes in a neurotoxic substate (green) kill oligodendrocytes and can also kill susceptible neurons (lavender). Microglia prune synapses and regulate neuronal excitability and in reactive states can aberrantly prune synapses and/or alter neuronal excitability. Cytokines from microglia and other sources can also alter synaptic function. Finally, reactive microglia-derived cytokines (e.g., IL6) as well as cytokines and chemokines from other sources (e.g., CCL11) impair hippocampal neurogenesis (purple). Figure created with BioRender.

In addition to these direct effects of inflammatory mediators on cellular plasticity in the brain, microglia also induce several different reactive states in astrocytes through cytokine signaling (for review, see Liddelow et al., 2020); the most well described is a neurotoxic reactive astrocyte sub-state described in rodents (Liddelow et al., 2017; Yun et al., 2018; Sterling et al., 2020; Guttenplan et al., 2021), and also occurring in humans (Barbar et al., 2020). Neuroinflammatory reactive astrocytes across a range of cellular states (Hasel et al., 2021; Sadick et al., 2022) can induce further pathophysiology, with certain states of reactive astrocytes inducing cell death of oligodendrocytes and of susceptible neurons (Guttenplan et al., 2021; Liddelow et al., 2017). The neurotoxic sub-state of reactive astrocytes does not adequately support synaptic connections, which can further add to circuit dysfunction (Liddelow et al., 2017) (Figure 2). This complex cellular dysregulation is thought to contribute importantly to cognitive impairment, and immune-modulatory strategies in mice correct such multicellular dysregulation and rescue cognition in disease states, such as occurs after exposure to neurotoxic cancer therapies (Geraghty et al., 2019; Gibson et al., 2019; Monje et al., 2003) and in aging (Villeda et al., 2011).

Clinical syndromes and scope of the COVID-19-related neurological health crisis

A wide range of persistent symptoms affect many who have been infected with SARS-CoV-2. Among the most common and most distressing long-term sequelae of COVID-19 are persistent cognitive symptoms. Studies of those infected early in the pandemic, chiefly with the ancestral strain of the virus, paint an alarming picture of an emerging neurological health crisis. A meta-analysis of 45 studies involving nearly 10,000 subjects found that more than 70% of people experience at least one symptom lasting more than 2 months after infection, with cognitive dysfunction affecting 25% of people, even those who had mild SARS-COV-2 infection (Nasserie et al., 2021). In a study of patients in Italy with COVID-19 pneumonia requiring hospitalization in the spring of 2020, neuropsychometric testing revealed impairment in at least one cognitive domain in 78% of patients at 3 months post-infection, with frequent cognitive impairments affecting psychomotor coordination (57%), executive function (50%), attention and information processing speed (33%), working memory (24%), and verbal memory (10%) (Mazza et al., 2021). Another neuropsychometric study examining all patients with mild, moderate, or severe COVID-19 in a New York City hospital system followed from spring of 2020 through spring of 2021, found impairment in attention (10%), processing speed (18%), memory encoding (24%), and executive function (16%) evident at 7 months after infection (Becker et al., 2021).

Cognitive impairment appears to persist long after COVID-19. Examination of individuals (154,068 diagnosed with COVID-19 from March 2020–January 2021 compared to 5,638,795 contemporary controls and 5,859,621 historical controls) in the US Veterans Affairs national healthcare database revealed elevated risk of cognitive and memory disorders (hazard ratio 1.77) and of a diagnosis of Alzheimer Disease (hazard ratio 2.03) in the 12 months following SARS-CoV-2 infection (Xu et al., 2022). Risk of cognitive disorders were evident in all subgroups analyzed regardless of age, sex, obesity, hypertension, hyperlipidemia, smoking history, or area deprivation index (Xu et al., 2022). Similarly, a 2-year retrospective cohort study using the TriNetX electronic health records network of 1,487,712 individuals with COVID-19 and a similar number of matched controls with a different respiratory infection found continued risk of cognitive impairment at 2 years from diagnosis (Taquet et al., 2022). In contrast to risk of cognitive impairment, the risk of anxiety and mood disorders normalized within 2 months following SARS-CoV-2 infection (Taquet et al., 2022). This TriNetX study provides some of the only available data about cognitive deficits in children and found that children did not exhibit an increased risk of anxiety or mood-disorder diagnoses but did exhibit increased risk of cognitive deficits (hazard ratio 1.2) and insomnia (hazard ratio 1.29) compared to children with different respiratory infections (Taquet et al., 2022). Unlike the adult cohort in this study, the risk of cognitive deficits in children normalized to the level observed in controls with a different respiratory infection by 491 days after having COVID-19 (Taquet et al., 2022).

Cognitive impairment can occur even after relatively mild illness during the acute phase of COVID-19. A landmark study of UK Biobank participants provides longitudinal cognitive assessment data in the same individuals before and after SARS-CoV-2 infection, including 401 participants before and after confirmed SARS-CoV-2 infection (15 of whom were hospitalized for COVID-19 and 386 who did not require hospitalization), compared to 384 matched control participants who did not contract COVID-19 during the study period. Neuropsychometric examination revealed a significant decline in cognitive function from their pre-COVID-19 baseline, as measured by trail-making tests A and B, in the group who had recovered from COVID-19. This result remained significant even when those individuals who had been hospitalized for COVID-19 were removed from the analysis (Douaud et al., 2022). While cognitive impairment can and does follow mild acute COVID-19, risk appears to be increased after severe acute illness. In both the New York study (Becker et al., 2021) and the Veterans Affairs study (Xu et al., 2022) discussed above, the incidence of cognitive impairment was found to be increased in hospitalized patients compared to those with more mild COVID-19; for example, processing speed was impaired in 18% of those with mild COVID-19, and in 28% of those who had COVID-19 severe enough to require hospitalization (Becker et al., 2021). Thus, while those with severe illness are at higher risk, people with even mild COVID-19 in the acute phase may experience lasting cognitive impairment (Becker et al., 2021; Tabacof et al., 2022; Douaud et al., 2022; Xu et al., 2022).

The incidence and severity of cognitive impairment following COVID-19 caused by newer SARS-CoV-2 variants, or as a result of breakthrough infection in vaccinated individuals, remains to be fully understood. Emerging data indicate that the risk of cognitive impairment may be decreased in breakthrough infections of fully vaccinated individuals, although this decrease appears to be relatively small and far less than one would hope. In a prospective, community-based case-control study using self-reported data, fully vaccinated (2 doses of an mRNA vaccine) individuals reported a small decrease (odds ratio ~0.8) in brain fog symptoms compared to unvaccinated individuals (Antonelli et al., 2022). Similarly, a study of 33,940 vaccinated (2 doses of an mRNA vaccine) individuals with breakthrough COVID-19 infection and 113,474 unvaccinated individuals with COVID-19 using the electronic healthcare database of the US Department of Veterans Affairs found the risk of long COVID to be reduced by only 15% in the vaccinated group, with a hazard ratio of 0.82 for risk of cognitive symptoms at 6 months post-infection (Al-Aly et al., 2022). Future work will be needed to clarify the extent to which prior vaccination may protect against the lasting neurological sequelae of COVID-19. Although there is limited data available for the sequelae with SARS-CoV-2 variants of concern, the data from the Office for National Statistics in the UK show that 4%–5% of the adults who are triple vaccinated develop self-reported long COVID after breakthrough infection with Delta (5%) and Omicron (4%), while 9% of double-vaccinated people self-report long COVID after infection with Delta compared to 4% of double-vaccinated people after infection with Omicron (https://www.ons.gov.uk, July 18, 2022 report). Whether each variant of concern manifests in similar neurological disease outcomes remains to be seen. The incidence and severity of cognitive symptoms after repeated infections also remains unclear. With over 600 million COVID-19 cases documented worldwide to date, the magnitude of the problem constitutes a neurological health crisis and demands an urgent effort to understand and develop interventions to mitigate or prevent COVID-19-associated cognitive impairment.

Human neuroimaging studies

The UK Biobank study discussed above compared magnetic resonance imaging (MRI) data before and after SARS-CoV-2 infection in 401 individuals and 385 matched controls. MRI data obtained an average of 141 days following COVID-19 diagnosis revealed widespread structural abnormalities, including a small but significant global decrease in brain volume, changes throughout the olfactory system, and structural abnormalities in the limbic system, cerebellum, and major white matter tracts (fimbria and superior fronto-occipital fasciculus) (Douaud et al., 2022). Concordant findings in an MRI study of individuals with persistent cognitive impairment after COVID-19 found white matter hyperintensities correlating with verbal memory deficits (Cecchetti et al., 2022). Another imaging and neuropsychological assessment of 223 individuals who recovered from mainly mild to moderate SARS-CoV-2 infections and 223 matched healthy controls found that among the 11 MRI markers tested, significant differences between groups were found in global measures of mean diffusivity and extracellular free water, which were both elevated in the white matter of post-SARS-CoV-2 individuals compared to matched controls. Increase in free-water and mean diffusivity could be an indirect sign of a prolonged neuroinflammatory response, and this increased free-water and mean diffusivity in the white matter of long COVID patients was proposed to reflect an activated local immune response involving microglia and astrocytes producing cytokines and inducing osmosis of water from the blood into the extracellular space (Petersen et al., 2022), a hypothesis supported by the cellular findings described below. However, in contrast to most other studies, neuropsychological test scores did not significantly differ between groups in this particular study (Petersen et al., 2022). While the neurosychological test results do not agree in all studies, these neuroimaging changes fit well with the histopathological findings discussed below involving the white matter, hippocampus (part of the limbic system), and cerebellum. Below, we will discuss pathological mechanisms that may contribute to these structural and functional changes in the nervous system following SARS-CoV-2 infection.

RESPIRATORY INFLAMMATION CAN CAUSE NEUROINFLAMMATION AND NEURAL DYSREGULATION

Immune challenges outside of the nervous system can result in profound and lasting neuroinflammation that can dysregulate cellular function in the brain. To assess the neurobiological effects of mild respiratory COVID-19, a mouse model of mild respiratory SARS-CoV-2 infection engineered to be restricted to the respiratory system (Israelow et al., 2020) was used. In this model, mice exhibited no discernable sickness behavior, did not lose weight, had no evidence of virus in brain tissue, and cleared the

virus from the respiratory system in about a week. This mild respiratory SARS-CoV-2 infection induced an immune response that resulted in persistently elevated cerebrospinal fluid (CSF) cytokines/chemokines and subcortical and hippocampal white matter microglial reactivity (Fernandez-Castaneda et al., 2022). Consistent with effects of reactive microglia in other disease settings (Geraghty et al., 2019; Gibson et al., 2019; Monje et al., 2003), impaired hippocampal neurogenesis, reduced numbers of oligodendrocyte precursor cells, reduced numbers of subcortical oligodendrocytes (by ~30%) and loss of myelinated axons (by ~10%) were evident in mice following mild respiratory SARS-CoV-2 infection for at least 7 weeks. It is important to note that the loss of myelinated axons was not in focal, plaque-like areas as would be expected for multiple sclerosis (MS)-like demyelination but rather distributed throughout white matter axons (Fernandez-Castaneda et al., 2022). Concordantly, focal areas of demyelination have not been common findings in COVID-19 post-mortem brain examinations (Thakur et al., 2021). Electron microscopy has not yet been done on human tissue post-COVID-19 to verify the mouse myelinated axon results in humans.

Similar to these findings in the mouse model of mild respiratory COVID-19, a hamster model of moderate COVID-19 (Frere et al., 2022; Soung et al., 2022) also exhibited microglial reactivity (Frere et al., 2022; Soung et al., 2022) and reduced neurogenesis in the hippocampus (Soung et al., 2022); oligodendrocytes and myelin have not been assessed yet in the hamster model. A reduction in immature neurons was confirmed in human hippocampus autopsy tissue from individuals who died from COVID-19 in comparison to control subjects (Soung et al., 2022). Taken together, these cellular findings are concordant with the structural abnormalities in white matter and in the limbic system detected on human neuroimaging discussed above.

Reactive microglia can inhibit neurogenesis directly through secretion of cytokines, such as IL6 (Monje et al., 2003; Vallieres et al., 2002), and can negatively influence myelinating oligodendrocytes in multiple ways, including indirectly by inciting neurotoxic astrocyte reactivity that can kill oligodendrocytes through toxic lipid secretion (Guttenplan et al., 2021) and by reducing neuronal brain-derived neurotrophic factor (BDNF) expression, which is required for the neuronal-activity-regulated oligodendrogenesis and myelin plasticity (Geraghty et al., 2019) that contributes to attention, memory, and learning (Geraghty et al., 2019; McKenzie et al., 2014; Pan et al., 2020; Steadman et al., 2020). Future work will determine if the microglial reactivity observed after mild respiratory COVID-19 is sufficient to induce neurotoxic astrocyte reactivity or other reactive sub-states that could have detrimental effects on the CNS without driving neuron/oligodendrocyte apoptosis, but this hypothesis would explain the magnitude of the observed oligodendrocytes loss (30%) within the first week after respiratory infection in this mouse model (Fernandez-Castaneda et al., 2022). The degree of myelinated axon loss after mild respiratory COVID-19 was similar to the loss observed in a mouse model of methotrexate chemotherapy-related cognitive impairment (Fernandez-Castaneda et al., 2022) in which microglial depletion restores myelination and rescues cognitive performance in behavioral tests (Geraghty et al., 2019; Gibson et al., 2019); experiments are ongoing to ascertain if similar microglial-targeting interventions may prove therapeutic after mild respiratory COVID-19 in mice. Taken together, these findings illustrate persistent cellular deficits after even mild respiratory COVID-19 that are predicted to influence cognitive function (Figure 2).

The white-matter-selective microglial reactivity evident after respiratory COVID-19 is a pattern observed in other disease contexts characterized by similar symptoms of cognitive impairment, such as cancer-related cognitive impairment (Gibson et al., 2019). Human brain samples from individuals who died with or after COVID-19 and who exhibited mild to moderate pulmonary injury, but not the necrotizing pneumonia characteristic of severe COVID-19, exhibited the same pattern of subcortical white-matter-enriched microglial reactivity, which was elevated in comparison to autopsy brain samples from control subjects with similar demographics and co-morbidities (Fernandez-Castaneda et al., 2022). Single-cell RNA sequencing of microglia after mild respiratory COVID-19 in mice revealed a small but prominent subpopulation of microglia in a transcriptional state that shared overlapping features with gene expression signatures of white-matter-associated microglia (WAM) observed in aging (Safaiyan et al., 2021) and disease-associated microglia (DAM) observed in Alzheimer's disease (Keren-Shaul et al., 2017), but this subpolulation of microglial cells also exhibited transcriptional changes characterized by chemokine expression not described in other disease contexts, highlighting aspects of a distinct state of microglial reactivity following COVID-19 (Fernandez-Castaneda et al., 2022). The functional consequences of this chemokine subpopulation of microglia should be further studied in future work.

Following mild respiratory COVID-19 in mice, pro-inflammatory CSF cytokines/chemokines were elevated for at least 7 weeks. Among the elevated cytokines and chemokines was CCL11, a chemokine associated with impairments in neurogenesis and cognition (Villeda et al., 2011) whose levels increased in the CSF between 7 days and 7 weeks post-infection (Fernandez-Castaneda et al., 2022), suggesting increased secretion from a CNS cell type over time. People experiencing long COVID following infection early in the pandemic in New York City who report persistent cognitive symptoms similarly demonstrate elevated CCL11 levels compared to those with long COVID lacking cognitive symptoms (Fernandez-Castaneda et al., 2022). In this cohort of individuals with long COVID, a history of autoimmune disease correlated with elevated CCL11 levels and cognitive symptoms (Fernandez-Castaneda et al., 2022). Systemic CCL11 administration to mice to directly test the effects of CCL11 resulted in microglial reactivity only in the hippocampus in this experimental paradigm, together with impaired hippocampal neurogenesis (Fernandez-Castaneda et al., 2022), indicating that certain cytokines and chemokines may exert region- and circuit-specific effects on microglia and other neural cell types or that certain brain regions may be differentially sensitive to particular cytokines and chemokines. Thus, while hippocampal microglial reactivity may be explained in part by elevated CCL11, the molecular mechanisms resulting in subcortical white matter microglial reactivity remain to be determined.

Comparing mild respiratory infection with SARS-CoV-2 to mild H1N1 influenza infection in mice revealed overlapping but

distinct CSF cytokine/chemokine profiles with the notable shared feature of persistently elevated CCL11 levels and a similar pattern of white-matter-selective microglial reactivity, oligodendrocyte loss, impaired hippocampal neurogenesis, and elevated CSF CCL11 levels at 1 week (Fernandez-Castaneda et al., 2022). By 7 weeks after influenza infection, subcortical white matter microglial reactivity and oligodendrocytes normalize, while elevated CSF CCL11 levels persist together with lasting hippocampal white matter microglial reactivity and impaired neurogenesis (Fernandez-Castaneda et al., 2022). Mild respiratory infection with H1N1 influenza thus results in similar hippocampal pathology but without the lasting effects on subcortical white matter integrity seen after respiratory COVID-19 (Fernandez-Castaneda et al., 2022). The similarities and differences evident between influenza—a disease also associated with neurological and neuropsychiatric sequalae (Honigsbaum 2013; Hosseini et al., 2018; Jurgens et al., 2012; Menninger, 1919)—and SARS-CoV-2 infections underscore the principle that the immune response to a respiratory infection can elicit neuroinflammation with downstream effects on neural-cell states and function.

These important downstream effects include not only the neurotoxic effects of microglia and astrocytes in certain reactive states but also the loss of neuro-supportive functions of these glial cell types in homeostatic states as discussed above. Similarly, altering the central nervous system immune milieu in the context of respiratory system inflammation-induced neuroinflammation could alter the neuro-supportive, neuroplasticity-promoting functions of other immune cells, such as gamma-delta T cells (Ribeiro et al., 2019) after COVID-19.

Unsurprisingly, neuroinflammation and glial dysregulation is particularly robust during the acute phases of severe COVID-19 (Cosentino et al., 2021). A study of CSF cytokine and chemokine levels in critically ill cancer patients with severe COVID-19 demonstrated cytokine/chemokine elevations commensurate with those seen in cytokine release syndrome during chimeric antigen receptor (CAR) T cell therapy for cancer (Remsik et al., 2021). In individuals who died from severe COVID-19 pneumonia, single-nucleus sequencing of medial frontal lobe cortical samples illustrates microglial reactivity, astrocyte reactivity, and the presence of T lymphocytes in the cortex (Yang et al., 2021). Concordant with the microglial transcriptional changes described above in mice following mild respiratory COVID-19, human microglia during severe COVID-19 exhibit a decrease in expression of homeostatic microglial genes and a transcriptional signature that partially overlaps with the DAM signature described in Alzheimer's disease—but that also exhibits distinct features indicative of a unique COVID-19-associated microglial cell state (Yang et al., 2021). It is of note that transcriptional signatures of DAM differ between mice and humans to some extent with overlapping but also distinct transcriptional features (Srinivasan et al., 2020). Choroid plexus samples from the same individuals revealed prominent inflammatory changes (Yang et al., 2021). Inflamed choroid plexus can transmit inflammatory signals to the brain (Baruch et al., 2014), and cell-cell communication analyses from this severe COVID-19 single nucleus sequencing study implied chemokine signaling from choroid plexus to cortical microglia, astrocytes, oligodendrocytes, and neurons, as well as complement signaling to cortical microglia (Yang et al., 2021). Whether this predicted complement-mediated signaling results in aberrantly increased synaptic pruning by microglia, as occurs in Alzheimer's disease (Hong et al., 2016) and in West Nile virus encephalitis (Vasek et al., 2016; Garber et al., 2019), remains to be determined. However, this important human brain single-nucleus sequencing study suggests a choroid plexus to cortical parenchyma relay of inflammation and glial dysregulation that may negatively influence cortical function in severe COVID-19. Whether similar choroid plexus inflammation occurs during or after milder COVID-19 and the extent to which such a brain-border-to-brain-parenchyma relay mechanism contributes to the persistent neuroinflammation observed after even mild respiratory-only infection remains to be determined in future work.

While this single-cell study of severe COVID-19 brain samples did not evaluate the white matter, an emerging pattern shows that white matter microglia, a distinct microglial subpopulation also called axon tract microglia (Hammond et al., 2019), are most sensitive to inflammatory stimuli and become reactive in response to the immune response to mild respiratory infection (Fernandez-Castaneda et al., 2022). As mentioned above, a sub-subpopulation of white matter microglia in the hilus of the hippocampal dentate gyrus assumes a reactive state in response to the chemokine CCL11 administered systemically (Fernandez-Castaneda et al., 2022). Subcortical white matter microglia do not respond in the same way to systemically administered CCL11 in the experimental paradigm used (Fernandez-Castaneda et al., 2022), further underscoring the regional heterogeneity of microglial responses. In more severe COVID-19, cortical microglia additionally become reactive (Yang et al., 2021). Whether choroid plexus inflammation is necessary or sufficient to trigger reactivity of either cortical or white matter microglial reactivity remains to be determined, and additional means of relaying peripheral inflammation to the brain include effects of circulating cytokines and chemokines, trafficking of immune cells to brain parenchyma through the vasculature or through the meningeal borders (Oliver et al., 2020), or afferent neural signaling such as the through the vagus nerve. Delineating the precise mechanisms by which respiratory inflammation triggers each aspect of neuroinflammation may be critical to develop therapeutic interventions to mitigate the effects of COVID-19 and other respiratory infections on the brain.

AUTO-IMMUNE MECHANISMS

Another mechanism by which COVID-19 may injure the nervous system is through autoimmunity. In a study of six individuals hospitalized for COVID-19 with acute neurological symptoms, including encephalopathy, headache, and seizures, single-cell transcriptomic analyses of immune cells in blood and CSF revealed activated T cells and clonal expansion of unique T cell clones in the CSF not found in blood, suggesting a compartmentalized T cell response to a CNS antigen (Song et al., 2021a). Enrichment of B cells was also found in the CSF of individuals with COVID-19 compared to control individuals, including distinct CSF plasma cell clusters and accordingly distinct

anti-SARS-CoV-2 antibodies in the CNS and peripheral compartments (Song et al., 2021a). Analyzing the antibodies isolated from patient CSF, antibodies reactive with neural antigens, including neuronal antigens, were found in the majority of subjects in this cohort (Song et al., 2021a). In another study involving 172 hospitalized patients with moderate and severe COVID-19, a diverse set of serum autoantibodies were found against vascular cells, coagulation factors and platelets, connective tissue, extracellular matrix components and various organ systems, including the central nervous system (Wang et al., 2021). Among this cohort, ten patients developed autoantibodies against HCRTR2, an orexin receptor that is enriched in the hypothalamus, with a marked negative correlation between levels of HCRTR2 autoantibodies and exceptionally low (poor) Glasgow coma scale scores. Concordant with this identification of anti-neuronal autoantibodies in patient CSF and sera in individuals with severe COVID-19 and prominent neurological symptoms, cases of autoimmune encephalitis have been reported (Payus et al., 2022). While autoimmune encephalitis clearly can and does occur, whether anti-neural antibodies occur commonly in mild to moderate COVID-19 and whether subclinical autoimmunity contributes to chronic neuroinflammation and lasting cognitive impairment remains to be determined. To this end, a recent study involving 215 participants over a year from SARS-CoV-2 infection, most of whom were not hospitalized, found no increase in autoantibodies to the human extracellular proteome in long COVID patients over convalescent and uninfected healthy control participants (Klein et al., 2022).

As can occur after many infections, rare cases of acute disseminated encephalomyelitis (ADEM), a monophasic, autoimmune inflammatory demyelinating disease, have been reported soon after COVID-19 (Parsons et al., 2020; Verriello et al., 2022). In contrast, an increased risk of multiple sclerosis diagnosis was not identified in a large population-based study (Zarifkar et al., 2022). Long-term follow-up studies are needed, as autoimmune outcomes may manifest at a much later time point.

DIRECT BRAIN INFECTION

Neuroinvasive infection could contribute to acute and chronic brain pathology through neuroinflammatory and cytotoxic mechanisms. Viral entry into a host cell depends on viral spike protein binding the cellular receptor ACE2 followed by proteolytic activation of spike by TMPRSS2 or Cathepsin L. Additional host factors may regulate entry and include neuropilin-1 (NRP1) (Cantuti-Castelvetri et al., 2020). The expression pattern of ACE2 indicates potential for viral entry in choroid plexus cells within the brain ventricles (Pellegrini et al., 2020) and pericytes throughout the cerebral microvasculature (Muhl et al., 2022) with low to no expression of ACE2 throughout the rest of the brain. *In vitro* tropism has been demonstrated for choroid plexus cells in organoid models (Pellegrini et al., 2020), neurons in organoid models (Song et al., 2021b), and astrocytes in human cortical organoids or acute fetal cortical slice preparations (Andrews et al., 2022). Furthermore, viral transmission can occur between cells through tunneling nanotubes connecting an infected epithelial cell and a neuron *in vitro* (Pepe et al., 2022). Given these multiple possible mechanisms of brain infection, cases of SARS-CoV-2 neuroinvasion have indeed been reported, with SARS-CoV-2 detected in the brains (Song et al., 2021b; Gomes et al., 2021; Matschke et al., 2020; Meinhardt et al., 2021) and olfactory epithelium (Meinhardt et al., 2021) of some patients at autopsy.

While direct brain infection can occur, durable infection appears to be uncommon (Cosentino et al., 2021). Many autopsy studies have found no evidence of SARS-CoV-2 in the brain (Lee et al., 2021; Yang et al., 2021; Thakur et al., 2021) or in the CSF of hospitalized patients with neurological symptoms (Alexopoulos et al., 2020; Remsik et al., 2021; Song et al., 2021a). Extensive PCR and immunohistochemical analyses of choroid plexus tissue from individuals who died from severe COVID-19 did not identify evidence of virus, but single-nucleus RNA sequencing in the same cases did reveal prominent choroid plexus inflammatory changes, including expression of the antiviral defense gene IFITM3, interferon, and complement cascade genes (Yang et al., 2021), perhaps indicating effective defense mechanisms. Antibodies against spike protein and other SARS-CoV-2 epitopes have been demonstrated in the CSF of patients with COVID-19 (Alexopoulos et al., 2020; Song et al., 2021a, 2021b), perhaps providing a clue as to how immune responses at the brain borders may protect susceptible, ACE2+ choroid plexus cells from infection with SARS-CoV-2 in most cases. Taken together, the available evidence suggests that direct CNS infection is rare and does not account for the majority of either acute or long-term neurological sequelae of COVID-19.

REACTIVATION OF LATENT HERPESVIRUSES

Healthy adult humans harbor multiple viruses, particularly the members of the Herpesviridae, in their latent state. These latent viruses do not cause any clinical disease at a steady state. However, acute viral infection can trigger the reactivation of these latent viruses, resulting in the production of infectious viral particles that can cause significant inflammation and symptoms. Epstein-Barr virus (EBV) is a highly prevalent γ-herpes virus that persistently infects over 90% of the human population (Dowd et al., 2013). A retrospective study of hospitalized COVID-19 patients in Wuhan, China during early 2020 found EBV reactivation in 55 of 217 patients. EBV reactivation was associated with age and female sex. Patients' early antigen (EA) IgG levels were significantly higher in non-survivors than in survivors (Meng et al., 2022). In a separate study, 66.7% (20/30) of long COVID patients versus 10% (2/20) of control subjects were positive for EBV reactivation based on positive titers for EBV EA-diffuse (EA-D) IgG or EBV viral capsid antigen (VCA) IgM (Gold et al., 2021). A deep multi-omic, longitudinal investigation of 309 COVID-19 patients from the initial diagnosis to convalescence (2–3 months later) found that EBV viremia at the time of COVID-19 diagnosis was one of the four predictive factors for long COVID development (Su et al., 2022). The study did not find cytomegalovirus (CMV) reactivation in their long COVID cohort. While SARS-CoV-2 RNAemia was also observed in patients with acute COVID-19, the development of persistent symptoms of fatigue and chronic sputum overproduction was specifically associated with EBV viremia. Consistently, a recent study demonstrated elevated IgG against EA-D, the EBV fusion

receptor component gp42, and minor VCA gp23 in long COVID patients using three orthogonal approaches (Klein et al., 2022). Notably, the IgG reactivity to EBV antigens correlated with populations of activated T cells, including IL4/IL6-producing Th2-like cells in long COVID patients.

Multiple studies in patients with ME/CFS have suggested an altered cellular immunity, including a Th2-skewed response that could result from the immune evasive strategies used by EBV-infected cells, which has been identified as a risk factor in a subset of ME/CFS patients (Ruiz-Pablos et al., 2021). Supporting a putative role for EBV reactivation in neurological and neuropsychiatric complications of COVID-19, the EBV protein deoxyuridine triphosphate nucleotidohydrolase (dUTPase) alone is sufficient to induce anxiety and sickness behaviors in mice (Aubrecht et al., 2014; Padgett et al., 2004), and a subset of patients with ME/CFS have increased serum levels of antibodies to the EBV dUTPase (Halpin et al., 2017). EBV infection is associated with multiple autoimmune diseases. EBV infection of autoreactive B cells can promote autoantibody secretion. In addition, Epstein-Barr nuclear antigen 2 (EBNA2) shows genome-wide occupancy of disease-associated loci for systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, type 1 diabetes, juvenile idiopathic arthritis, and celiac disease (Harley et al., 2018). Taken together, EBV may contribute to neuroinflammation in long COVID patients due to viral pathogenesis (viral proteins and viral transcription factors) and/or host immune response to EBV infection (cytokines, Th2 responses, and autoantibody production).

Another important Herpesviridae is herpes simplex virus (HSV) type 1 and 2. HSV reactivation can result in herpes encephalitis, a life-threatening brain infection classically involving medial temporal lobe structures such as the hippocampus that can manifest as behavioral changes, seizures, and altered levels of consciousness. In rare cases, herpes encephalitis has occurred within weeks following COVID-19 diagnosis (Gupta et al., 2022) and may relate in part to the lympho-suppressive effects of corticosteroid use during management of COVID-19. This severe complication of COVID-19 requires urgent management with anti-viral medications such as acyclovir and supportive care and may result in irreversible injury to the hippocampus and other affected brain structures. In the Columbia autopsy series discussed below, one of the 41 subjects examined exhibited disseminated HSV-1 with brain involvement (Thakur et al., 2021). While IgG reactivities to HSV antigens were lower in long COVID patients, similar to EBV, IgG levels against varicella-zoster virus glycoprotein antigens were also elevated in long COVID patients (Klein et al., 2022). These data suggest that certain herpesvirus reactivation is somehow more frequent in those who develop long COVID and provide clues for possible interventions.

COVID-19-ASSOCIATED COAGULOPATHY AND CEREBRAL VASCULOPATHY

COVID-19 increases the risk of ischemic stroke (Zarifkar et al., 2022; Xu et al., 2022) and other thrombotic complications (Greuel et al., 2021), underscoring the potential thrombotic and vascular effects of COVID-19 on the brain. In a New York City hospital (Columbia)-based autopsy study of 41 individuals who died from severe COVID-19 in the acute or subacute phase of the disease, both hemorrhages (8/41) and ischemic infarcts (18/41) were observed commonly in the brains examined, as were global or focal hypoxic changes (41/41) (Thakur et al., 2021). A population-based cohort study of nearly 3 million people in Denmark sheds further light on the influence of respiratory infections on risk of neurological diseases and the particularly thrombogenic effects (for review, see Conway et al., 2022) of COVID-19. This study included ~43,000 people who tested positive for COVID-19 between February 2020 and November 2021 and a comparison cohort of individuals hospitalized with influenza A or B (~8,000 people), or bacterial, community-acquired pneumonia (~1,400 people). In those with COVID-19 that did not require hospitalization, risk of subsequent diagnosis of Alzheimer's disease, Parkinson's disease, ischemic stroke, and intracerebral hemorrhage in the 12 months that followed COVID-19 diagnosis was increased compared to those without a history of COVID-19 (Zarifkar et al., 2022). In people with acute disease severe enough to require hospitalization, those with COVID-19 exhibited an increased relative risk of ischemic stroke compared to those hospitalized for influenza (Zarifkar et al., 2022). Thus, ischemic stroke was the only disease that was more common after COVID-19 than other respiratory infections, while respiratory infections in general conferred an increased risk of neurodegenerative and cerebrovascular diseases (Zarifkar et al., 2022), an increased risk that may relate to the respiratory infection-induced neuroinflammation discussed above.

Certainly, ischemic strokes can confer lasting neurological sequelae and impair cognitive functions in a vascular-territory-dependent manner. Small vessel thromboses and vascular dysfunction including blood-brain-barrier disruption can also influence neurological function in subtle but debilitating ways. This increased risk of thrombosis is consistent with studies demonstrating fibrin microclots and activated platelets in the blood of patients with long COVID (Pretorius et al., 2022). Autopsy examination of nine individuals who died suddenly with or after SARS-CoV-2 infection in the spring of 2020 and who exhibited no evidence of SARS-CoV-2 infection in brain tissue (Lee et al., 2021) revealed microvascular injury and endothelial cell activation with perivascular leakage of the large plasma protein fibrinogen, indicative of blood-brain-barrier dysfunction, found throughout the brain and most prominent in the hindbrain (cerebellum and brainstem) (Lee et al., 2022). How reactivity of astrocytes, as discussed above, may contribute to this dysfunction of the blood-brain-barrier—to which homeostatic astrocytes critically contribute—remains to be determined. Together with this parenchymal fibrinogen around small vessels were perivascular inflammatory infiltrates composed of microglia/macrophages, $CD8^+$ T cells and perivascular astrocyte reactivity as measured by increased glial fibrillary acidic protein (GFAP) immunostaining (Lee et al., 2022), consistent with the pro-neuroinflammatory effects of fibrinogen (for review, see Petersen et al., 2022). Within small vessels, occlusive and non-occlusive microthrombi were observed throughout the small vessels of the brain, meninges, and choroid plexus, again more prominently in hindbrain than forebrain. Immune complexes containing antibodies and complement cascade components were found adherent to endothelial cells within small vessels (Lee et al., 2022). Scattered neuronal loss with microglial neuronophagia

was found, especially in the cerebellum and brainstem where microglial nodules have been reported to be more prominent (Lee et al., 2021, 2022; Matschke et al., 2020; Thakur et al., 2021). Despite this small vessel disease, micro-infarcts were rare in this cohort of patients (Lee et al., 2022), in contrast to the findings in patients who died in the hospital of severe COVID-19 in whom infarcts were common (Thakur et al., 2021). Whether this microglial neuronophagia is causing neuronal cell death, or rather is in reaction to neuronal cell death caused by another mechanism, such as toxic lipids from neurotoxic reactive astrocytes (Guttenplan et al., 2021) or other astrocyte-connected neuron cell death methods (e.g., glutamate excitotoxicity), remains to be determined.

HYPOXIA AND OTHER ASPECTS OF CRITICAL ILLNESS

Hypoxia, hypotension, metabolic disturbances from multi-organ failure, and polypharmacy during critical illness can all contribute to lasting cognitive symptoms. Critical illness in general is associated with a high rate of persistent cognitive impairment, which is an important component of post-intensive care syndrome (PICS) (Pandharipande et al., 2013). Given the profound effect of COVID-19 on the lungs in moderate to severe cases, hypoxia is common during the acute phase of the disease, and hypoxic changes are evident in the brains of individuals who died of severe COVID-19 (Thakur et al., 2021). Certain neural cell populations, particularly subtypes of neurons such as CA1 layer hippocampal pyramidal neurons, are exquisitely sensitive to hypoxia and this may render certain cells more susceptible to other effects of COVID-19 on the brain, such as inflammation-induced astrocyte reactivity. For example, hypoxia due to effects of COVID-19 in the lungs might render neurons more susceptible to the toxic lipids produced by neurotoxic sub-states of astrocytes (Guttenplan et al., 2021), which in turn is induced by reactive microglia responding to inflammatory signals triggered by the respiratory infection. While this hypothesis requires testing, it is this sort of complex interplay between the possible mechanisms of COVID-19-induced brain injury that may explain the increased rate and severity of chronic neurological complications in people who survived more severe acute disease.

CONCLUDING THOUGHTS AND FUTURE DIRECTIONS

Neurocognitive and neuropsychiatric impairments experienced by people with both acute and long COVID (neuro-COVID) have led to decline in quality of life and inability to return to previous levels of occupational function, affecting (at least) tens of millions of people. We highlight a number of possible underlying disease mechanisms that could contribute to CNS dysfunction, including neuroinflammatory effects of distal inflammation, autoimmunity, direct CNS infection, herpesvirus reactivation, neurovascular disease, and hypoxia. What accounts for the persistent nature of cognitive dysfunction in neuro-COVID remains to be fully elucidated. Continuing neuroinflammation could reflect a lasting state change in CNS immune and glial cells that perpetuates neural pathophysiology, ongoing endotheliopathy with microvascular disruption and blood-brain-barrier breakdown, autoimmunity, response to ongoing peripheral inflammation— attributable to latent herpesvirus reactivation (Su et al., 2022), possible persistent reservoirs of SARS-CoV-2 infection outside of the nervous system (Gaebler et al., 2021; Tejerina et al., 2022), or persistent circulating spike protein (Swank et al., 2022)—or a combination of these possibilities. A deeper mechanistic understanding of the pathophysiology of long COVID in general and neuro-COVID in particular will be required to develop effective therapies to ease the suffering of millions of people affected by the often-debilitating long-term consequences of COVID-19.

Advances in neuroscience, glial biology, immunology, and the intersection of these fields have laid important groundwork in understanding neuro-COVID. Lessons from cancer-therapy-related cognitive impairment, aging, and neurodegenerative disease studies are particularly instructive and highlight emerging common principles that will accelerate understanding and the development of therapeutic interventions for neuro-COVID. Similarly, scientific progress in the areas of acute respiratory distress syndrome, sepsis, and cancer immunotherapy helped identify the role of cytokine storm in the pathophysiology of severe COVID-19. These advances highlight the need for both multidisciplinary collaboration and for investment and support for basic science research in all disease areas.

In the future, basic insights will inform therapies that can be tested in randomized clinical trials. For instance, therapies that show promise in the treatment of cancer-therapy-related cognitive impairment (Riggs et al., 2017; Gibson et al., 2019; Geraghty et al., 2019; Ayoub et al., 2020) should be tested for neuro-COVID. Strategies to reset microglia to homeostatic, non-reactive states are urgently needed and would benefit a wide range of neurological disorders. Specific anti-cytokine and anti-chemokine agents may also prove therapeutically useful. Alternatively, strategies to promote mechanisms of neural plasticity despite ongoing neuroinflammation may also alleviate cognitive symptoms. If inflammation is caused by persistent virus infection or viral remnants in the lung, intestinal tract, and other reservoirs, vaccines and antiviral therapies should be able to help alleviate the neurological long COVID burden by removing the source cause of distal inflammation. On the other hand, immunosuppressive or immunomodulatory treatments may be needed to block autoimmune T and B cells. Neurovascular disease and thrombosis may require careful use of anticoagulants and thrombolytics. Biomarkers are needed to determine who will benefit from each of these potential therapeutic strategies, and clinical trials are urgently needed to test the safety and efficacy of potential therapeutic interventions for neuro-COVID.

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AUTHOR CONTRIBUTIONS

M.M. and A.I. wrote and edited the manuscript.

DECLARATION OF INTERESTS

M.M. holds equity in MapLight Therapeutics and Syncopation Life Sciences. A.I. holds equity in RIGImmune and Xanadu Bio. M.M. is on the advisory board for *Neuron*.

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